IS ORAL MIFEPRISTONE AS EFFECTIVE AS VAGINAL PROSTAGLANDIN E2 IN PRE INDUCTION CERVICAL RIPENING AT TERM GESTATION IN NORMAL AND UNCOMPLICATED PREGNANCIES?

DISSERTATION SUBMITTED IN FULFILLMENT OF THE REGULATIONS FOR THE AWARD OF

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THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

GUINDY, CHENNAI, TAMILNADU, INDIA

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DECLARATION

I hereby declare that this dissertation entitled "**IS ORAL MIFEPRISTONE AS EFFECTIVE AS VAGINAL PROSTAGLANDIN E2 IN PRE INDUCTION CERVICAL RIPENING AT TERM GESTATION IN NORMAL AND UNCOMPLICATED PREGNANCIES?**" was prepared by me under the direct guidance and supervision of **Prof. Dr. Kanchanamalai MD OG.,** PSG Hospitals, Coimbatore.

The dissertation is submitted to the Dr. M.G.R. Medical University in partial fulfillment of the University regulations for the award of MD degree in Obstetrics and Gynaecology. This dissertation has not been submitted for the award of any Degree or Diploma.

Certificate

CERTIFICATE

This is to certify that **Dr. P. Uma devi** has prepared this dissertation entitled **" IS ORAL MIFEPRISTONE AS EFFECTIVE AS VAGINAL PROSTAGLANDIN E2 IN PRE INDUCTION CERVICAL RIPENING AT TERM GESTATION IN NORMAL AND UNCOMPLICATED PREGNANCIES?"** under my overall supervision and guidance in the Institute of PSG Institute of Medical Science and Research, Coimbatore in partial fulfillment of the regulations of Tamil Nadu **Dr. M.G.R. Medical University** for the award of **M.D. Degree in Obstetrics and Gynaecology.**

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Introduction

INTRODUCTION

Induction of labor implies the artificial initiation of uterine contractions prior to their spontaneous onset beyond the period of viability. Induction of labor is indicated when the benefits of termination of pregnancy to the mother or the fetus outweighs those of continuing pregnancy. Labor induction is a clinical intervention that has the potential to confer major benefits to the mother and newborn.

The history of labor induction dates back to Hippocrates' original descriptions of mammary stimulation and mechanical dilation of the cervical canal [1]. During the second century AD, Soranus practiced a combination of procedures to induce labor, including artificial rupture of the membranes. Other labor induction methods were introduced during this period; Moshion was the first to describe manual dilation of the cervix, and Casis invented several instruments capable of cervical dilation.

Midway through the 16th century, Paré devised a technique that combined manual cervical dilation and internal podalic version in patients with uterine hemorrhage [2]. Bourgeois, a disciple of Paré, continued this practice and also induced and augmented labor with strong enemas and mixtures of several folk medicines [3]

From the 2nd through the 17th centuries, mechanical methods to induce labor came into more common use. In 1756, at a meeting held in London, physicians discussed the efficacy and ethics of early delivery by rupturing the membranes to induce labor [4].

In 1810, James was the first in the United States to utilize amniotomy to induce premature labor [5]. Amniotomy and other mechanical methods remained the methods of labor induction most commonly employed until the 20th century.

In 1906, Dale observed that extracts from the infundibular lobe of the pituitary gland caused myometrial contractions [6].Three years later; Bell reported the first experience with use of a pituitary extract for labor induction [7].With the introduction of pituitary extract as a hormonal method of labor induction in 1913, the use of this method gained acceptance among obstetricians. However, due to the use of large doses and the impurity of the extract, numerous adverse effects were reported. Gradually, as the number of reported cases of uterine rupture increased, pituitary extract became discredited in many centers.

Initially, oxytocin (pituitary extract) was administered via intramuscular or subcutaneous routes. In 1943, Page suggested that the pituitary extract oxytocin be given in the form of an intravenous infusion [8] and in 1949; Theobald reported his initial results with this form of administration [9]. Fourteen years later in 1953, the structural formula of oxytocin was discovered, and synthetic oxytocin has been in use since 1955.

In 1968, Karim and colleagues were the first to report the use of prostaglandins for labor induction [10]. Since then, the use of prostaglandins, in different varieties and forms of administration, has become a common method of labor induction [11]. More recently, the synthetic prostaglandin analogue misoprostol has gained acceptance as an effective and safe method of labor induction [12].

Induction of labor is common in obstetric practice. According to the most current studies, the rate of induction varies from 9.5 to 33.7 percent of all pregnancies annually [18]. In the absence of a ripe or favorable cervix, a successful vaginal birth is less likely.

The amount of uterine pressure to dilate a ripe cervix is thought to be approximately 1600 mm Hg, while the pressure to dilate an unripe cervix is estimated to be greater than 5 times that, or 10,000 mm Hg. Therefore, cervical ripening or preparedness for induction should be assessed before a regimen is selected. Assessment is accomplished by calculating a Bishop score.

Cervical ripening usually begins prior to the onset of labor contractions and is necessary for cervical dilatation and the passage of the fetus. Cervical ripening is the result of a series of complex biochemical processes that ends with rearrangement and realignment of the collagen molecules. The cervix thins, softens, relaxes, and opens in response to uterine contractions, which pull the cervix over the presenting fetal part. Cervical ripening is the result of realignment of collagen, degradation of collagen cross-linking due to proteolytic enzymes, and dilatation resulting from these processes plus uterine contractions.

The most commonly used methodology to evaluate cervical ripening is the Bishop score because it is simple and has the most predictive value. This score uses cervical dilatation, effacement, consistency, position, and the station of the presenting part

BISHOP SCORE

Bishop Scoring System [27]					
Factors					
Score	**Dilation (cm)**	**Effacement (%)**	**Station***	**Cervical Consistency**	**Position of Cervix**
0	**Closed**	**0-30**	**-3**	**Firm**	**Posterior**
1	**1-2**	**40-50**	**-2**	**Medium**	**Mid position**
2	**3-4**	**60-70**	**-1,0**	**Soft**	**Anterior**
3	**5-6**	**80**	**+1,+2**	**--**	**--**
***Station reflects a. 3 to +3 scale.**					
Modified from Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol 1964;24:267					

A Bishop score of 6 or more is considered significant for cervical ripening and favorable for induction of labor.

When the Bishop score is less than 6, it is recommended that a cervical ripening agent be used before labor induction [63].

Numerous pharmacological and non pharmacological methods of labor induction are available .Non pharmacologic approaches to cervical ripening and labor induction have included herbal compounds, castor oil, hot baths, enemas, sexual intercourse, breast stimulation, acupuncture, acupressure, transcutaneous nerve stimulation, and mechanical and surgical modalities. Of these non pharmacologic

methods, only the mechanical and surgical methods have proven efficacy for cervical ripening or induction of labor [18].

Pharmacologic agents available for cervical ripening and labor induction include prostaglandins, misoprostol, mifepristone, and relaxin. When the Bishop score is favorable, the preferred pharmacologic agent is oxytocin.

In the current standard of care PGE2 gel is routinely used as an induction agent. This is a currently accepted standard of care. Its efficacy and safety as an induction agent has been proven by many studies. Even though it is a standard means of care in labor induction, common problems encountered in day to day practice in applying this induction agent like

Patient needs to be admitted

Drug application (intracervically) is cumbersome to the patient

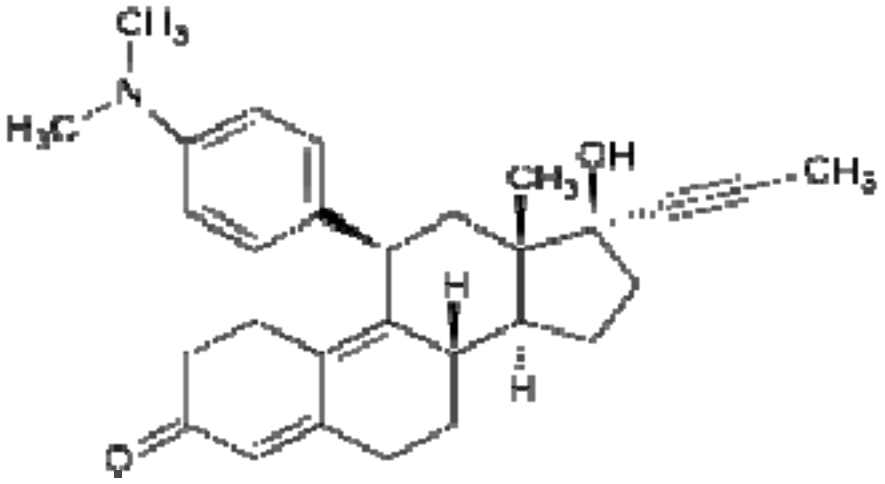
Needs the availability of an expert

If there is an orally available induction agent which can be administered orally the above mentioned problems can be easily overcome. This gains importance in day to day practice especially in obstetrics departments where admissions can be minimized especially where there is an increased need for pressure of beds. If an oral induction agent is available the patient assessment can be made in OPD and induction can be made as an op procedure and the patient can be asked to get admitted after allowing sufficient time for cervical ripening and effacement.

This practice is well implemented in western countries and requires the necessity to be implemented in our country also put forth. This is also convenient to

the patient as the hospital stay is considerably reduced. The search for this kind of induction agent has been going on for a considerable period of time and various induction agents like misoprostol have been tried so far.

MIFEPRISTONE



IUPAC name

11β-[p-(Dimethylamino) phenyl]-17β-hydroxy-17-(1-propynyl) estra-4, 9-dien-3-one

Mifepristone blocks the effect of progesterone by acting on the progesterone receptors. Progesterone is necessary for the establishment and maintenance of pregnancy in women. It also causes relaxation of the myometrium and leads to the prevention of myometrial contraction. With its anti progesterone effects, mifepristone prevents progesterone from exerting its action. It also blocks receptors for other steroids, including androgens and also increases the production of prostaglandins by the uterine lining during pregnancy. The blockade of progesterone effects and the stimulation of prostaglandins increase uterine contractility. Blood levels of

mifepristone peak within 2 hours after oral dosage, decreases by half over 20 hours, and are excreted mainly in bile.

In late pregnancy, the uterus is sensitized by mifepristone to prostaglandins and promotes cervical dilatation which induces labor. p receptors in the placenta are also blocked by mifepristone effectively, resulting in the termination of pregnancy. Thus, Mifepristone appears to be efficacious, safe and adds valuable alternatives to the cervical ripening and labor induction

Review of Literature

REVIEW OF LITERATURE

The Cochrane based review of mifepristone in Cochrane database 2009 [30] says the female steroid sex hormone, progesterone, inhibits contractility of the uterus. A new class of pharmacological agents (anti progestin) has been developed to antagonize the action of progesterone. Of these mifepristone also called as RU486 is best known. Mifepristone, a 19 nor steroid which has greater affinity for progesterone receptors than does progesterone itself. It thus blocks the action of progesterone at the cellular level. The pharmacokinetics of mifepristone is characterized by rapid absorption and a long half life of 25 to 30 hours (Heikinheimo 1997) [26]. Key metabolites also have high affinity to progesterone receptors

Mifepristone now has an established role in termination of pregnancy (in combination with prostaglandins) during the early first, and the second trimesters (Van look 1995)[34]. Mifepristone is also being investigated as a possible contraceptive agent.

Mifepristone has potential also as a method of inducing labor in late pregnancy, through its actions in antagonizing progesterone, and thus increasing uterine contractility. Mifepristone has been shown to induce labor in rats (FANG 1997) [43], through opposition to progesterone – induced suppression of oxytocin receptors, and enhanced synthesis of prostaglandins. Mifepristone has also been shown to induce preterm birth in mice, associated with a rise in prostaglandins and cytokines (Dudley 1996) [42]

A randomized controlled trial in beef heifers found a mean time to delivery of 43 hours after mifepristone administration, compared to 182 hours in placebo treated

controls (Dlamini 1995); interestingly, retained placenta was a problem in the experimental group. In a primate model (the macaque), mifepristone administration induced prostaglandin F2 alpha production by decidua, but not prostaglandin E2 production by amnion (haluska 1994) [26]

There is thus, reason to anticipate from animal studies and termination studies in human pregnancies that mifepristone might prove an effective method of inducing labor in late human pregnancy.

In 2000, Wing DA et al [29] in their study reported that 54 percent normal women given 200 mg Mifepristone daily for two consecutive days went into labor within 72 hours compared with only 18.2 percent of those given a placebo.

A prospective study done by McGill J et al United kingdom 2007 [16] showed that the rate of caesarean section was significantly lower among women induced with mifepristone alone. Another study from Sweden, department of women and child health says that the median time taken from the onset of treatment unto delivery is relatively lower in groups with mifepristone than the control group.

A study from France, department of obstetrics and gynecology, Clamart [15] says that mifepristone appears safe and useful with no adverse effects on the fetus or the mother. Another study by Michel J Fassett et al from Los angles, California, USA [29] says that oral mifepristone administration to women with pregnancies beyond 41 weeks increases uterine activity in the absence of externally administered uterotonic agents. A similar study from USA says Mifepristone is proved effective for cervical ripening and reduced the time to delivery compared with placebo.

A randomized controlled study, by Berkane and associates in 2005 [28] on the effectiveness of mifepristone for ripening the cervix and inducing labor in term pregnancies among 346 women stated that mifepristone was well tolerated by the mother and fetus without any adverse outcomes.

A randomized double-blind trial by Frydman et al [13] employing 200 mg of mifepristone daily for 2 days resulted in a shorter interval to the onset of labor, and less oxytocin was required for those achieving vaginal delivery. In the mifepristone group, 58% went into spontaneous labor, compared with 22.6% in the placebo group.

Elliot [14] and colleagues compared the effects of 50 mg and 200 mg of oral mifepristone with placebo on cervical ripening and labor induction in primigravid women with unfavorable cervices at term. At a dose of 200 mg, mifepristone resulted in a favorable cervix or spontaneous labor more often than did placebo. Another randomized control trial by Giacalone [22] et al from France also proved that mifepristone is effective for cervical ripening and reduced the time to delivery when compared with placebo

A retrospective study by Gallot [14] et al from France compared the mode of delivery in two groups where labor was induced with mifepristone .It concluded that mifepristone was successful in inducing labor spontaneously in over 50% of pregnancies after 41 weeks of gestation.

A randomized control trial done by Wing DA [29]et al in university of south California among 180 antenatal women for preinduction cervical ripening beyond 41 weeks of gestation said that mifepristone had a modest effect on cervical ripening

when given 24 hours before labor induction, appearing to reduce the need for misoprostol and oxytocin compared with placebo.

Aim & Objective

AIM OF THE STUDY

- To compare the effect of oral mifepristone as a pre induction cervical ripening agent at term gestation age in normal and uncomplicated pregnancies when compared to vaginal prostaglandin E2
- To compare improvement of bishop score following induction
- To compare the induction delivery time interval
- To compare the maternal and fetal outcomes
- To compare the rate of fetal distress following delivery

Materials & Methodology

MATERIALS AND METHODS

All term antenatal patients who are coming for checkup / delivery in PSG Hospitals – Labor ward were included in the study. The study was a prospective case control study with one hundred and twenty women was included in the study from June 2009 to December 2010.

SELECTION CRITERIA

Antenatal women between 37 completed weeks of gestation upto 42 weeks of gestation with singleton pregnancies and cephalic presentation, with an unripe cervix (Bishop Score </= 4) with no medical complications warranting immediate delivery.

INCLUSION CRITERIA

- Term gestational age
- Reactive fetal heart rate pattern
- Pre induction bishop score < 4

EXCLUSION CRITERIA

- Premature rupture of membranes
- Oligohydramnios
- Multiple pregnancies
- Medical complications of pregnancy where delivery is urgent
- Previous LSCS
- Post term pregnancy

METHODOLOGY

The antenatal patient comes to labor ward where a basic assessment for risk factors is made and if the patient fits into the criteria of uncomplicated term gestation with bishop score of < 4 then she is entered into the study and the researcher is informed. The researcher after verifying the inclusion and exclusion criteria confirms inclusion of the patient into the study. The patients were randomly allocated (by sealed envelope method) into study group and control group.

STUDY GROUP

In the study group following a basic pelvic assessment (to rule out cephalopelvic disproportion) and reactive Non stress test - bishop score is assessed. If the score is < 4 (unfavorable cervix) pre induction cervical ripening done with oral T.Mifepristone 200mg stat. The patient is under observation for the spontaneous onset of labor or draining PV or reassessed after 48 hours – whichever is earlier. Labor was defined by effective uterine contractions with gradual cervical modifications.

Those patients who did not go into labor were reassessed after 48 hours. A post induction bishop score of > 6 is favorable and says that the induction agent is successful. The method of further induction is decided and implemented according to the Bishop score.

CONTROL GROUP

In the control group following a basic pelvic assessment (to rule out cephalopelvic disproportion) and a Non stress test is done and Bishop score is assessed. If the score is < 4 (unfavorable cervix) and NST is reactive PGE2 gel is

applied intracervically. The patient is reassessed after spontaneous onset of labor or draining PV or after 12 hours – whichever is earliest. A post induction bishop score of > 6 is favorable and says that the induction agent is successful. The method of further induction is decided and implemented according to Bishop score.

In the interval period fetal heart rate monitoring is done to assess the fetal well being.

Abnormal FHR patterns were defined as the presence of fetal tachycardia or bradycardia, late decelerations or moderate to severe FHR decelerations.

The pre and post induction assessment will be made by equally skilled assessors of the same designation.

Results & Analysis

RESULTS AND ANALYSIS

In our study all term antenatal patients who were booked at PSG Hospitals or unbooked were included in the study. The study was a prospective case control study with one hundred and twenty women included in the study from June 2009 to December 2010.

Women with previous caesarean births, post term pregnancies, PROM and medical complications warranting immediate delivery were excluded from the study.

This clinical study with 60 patients in the study group and 60 in the control group was undertaken to study the Assessment of bishop score, mean duration of labor induction, efficacy for cervical ripening and as an induction agent, rate of vaginal deliveries, incidence of fetal distress, rate of caesarean section and their indication and rate of NICU admission.

Statistical data analysis was calculated using SPSS software

ANALYSIS

TABLE 1

AGE DISTRIBUTION OF PATIENTS IN TWO GROUPS

Age in years	Study Group		Control group	
	No	%	No	%
18-20	14	23.3	10	16.7
21-25	24	40.0	29	48.3
26-30	14	23.3	19	31.7
>30	8	13.3	2	3.3
Total	60	100.0	60	100.0
Mean ± SD	24.75±4.17		24.07±3.08	

Samples are age matched with p=0.309

The age differences are similar and comparable in the study and control group

Fig 1. AGE DISTRIBUTION OF PATIENTS IN TWO GROUPS

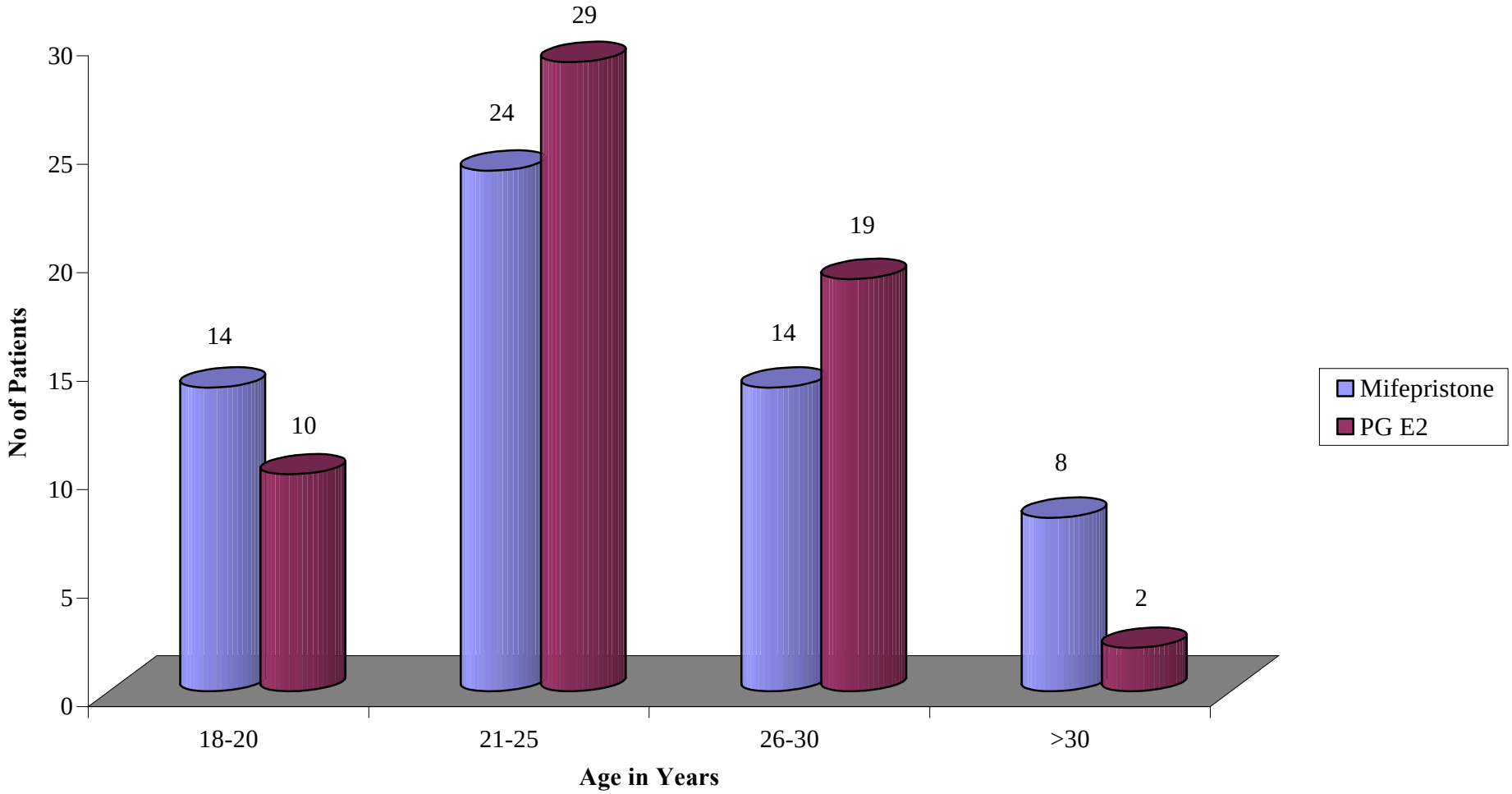


TABLE 2

GESTATIONAL AGE IN WEEKS

Gestational age in weeks	Study Group		Control group	
	No	%	No	%
37	9	15.0	5	8.3
38	18	30.0	21	35.0
39	19	31.7	15	25.0
40 & above	14	23.3	18	30.0
Total	60	100.0	60	100.0
Mean ± SD	38.65±1.04		38.78±0.98	

p=0.486

The Gestational age is statistically similar between two groups

Fig 2. GESTATIONAL AGE IN WEEKS

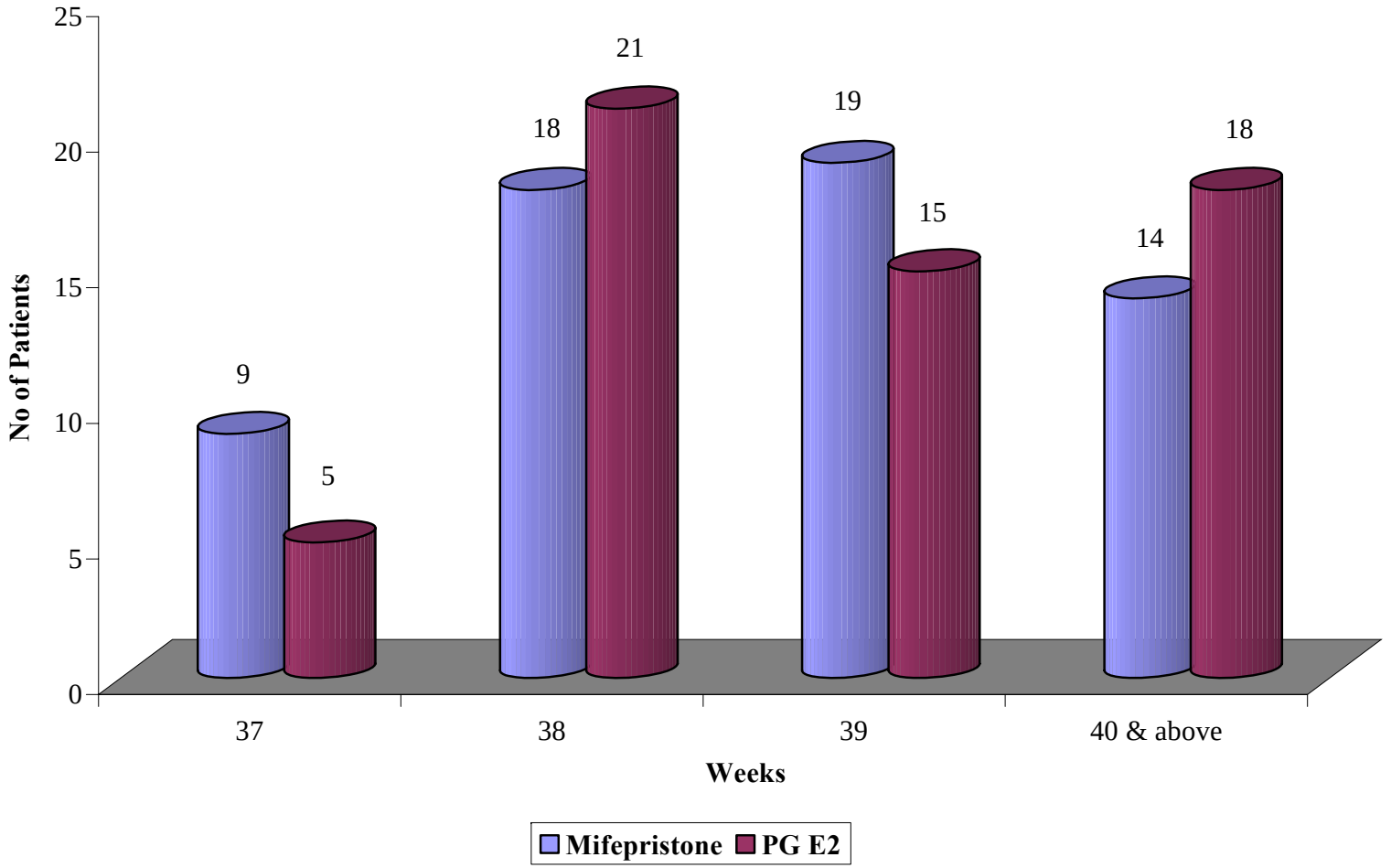


TABLE 3

PARITY STATUS OF PATIENTS IN TWO GROUPS

	Study Group		Control group	
	No	%	No	%
Nullipara	48	80	44	73.3
Para 1	11	18.3	16	26.6
Para > 1	1	1.6	-	-
Total	60	100.0	60	100.0

The parity status was comparable in both groups

Fig 3. PARITY STATUS

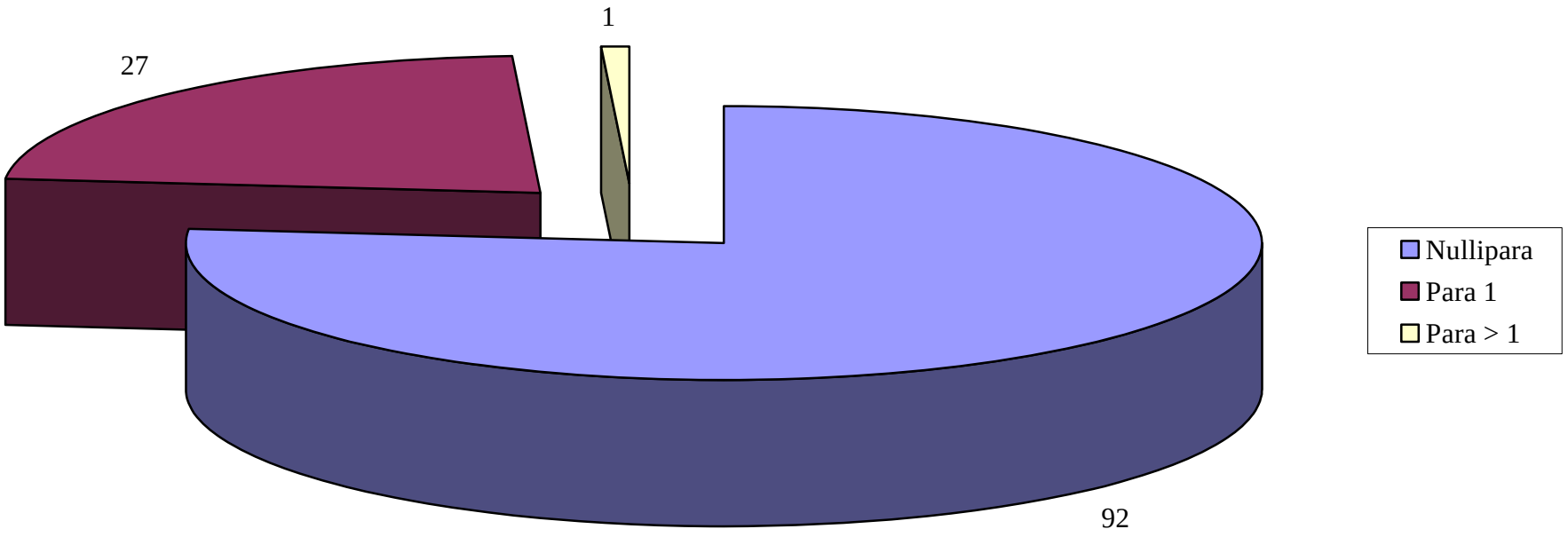


Fig 4. PARITY STATUS OF PATIENTS IN TWO GROUPS

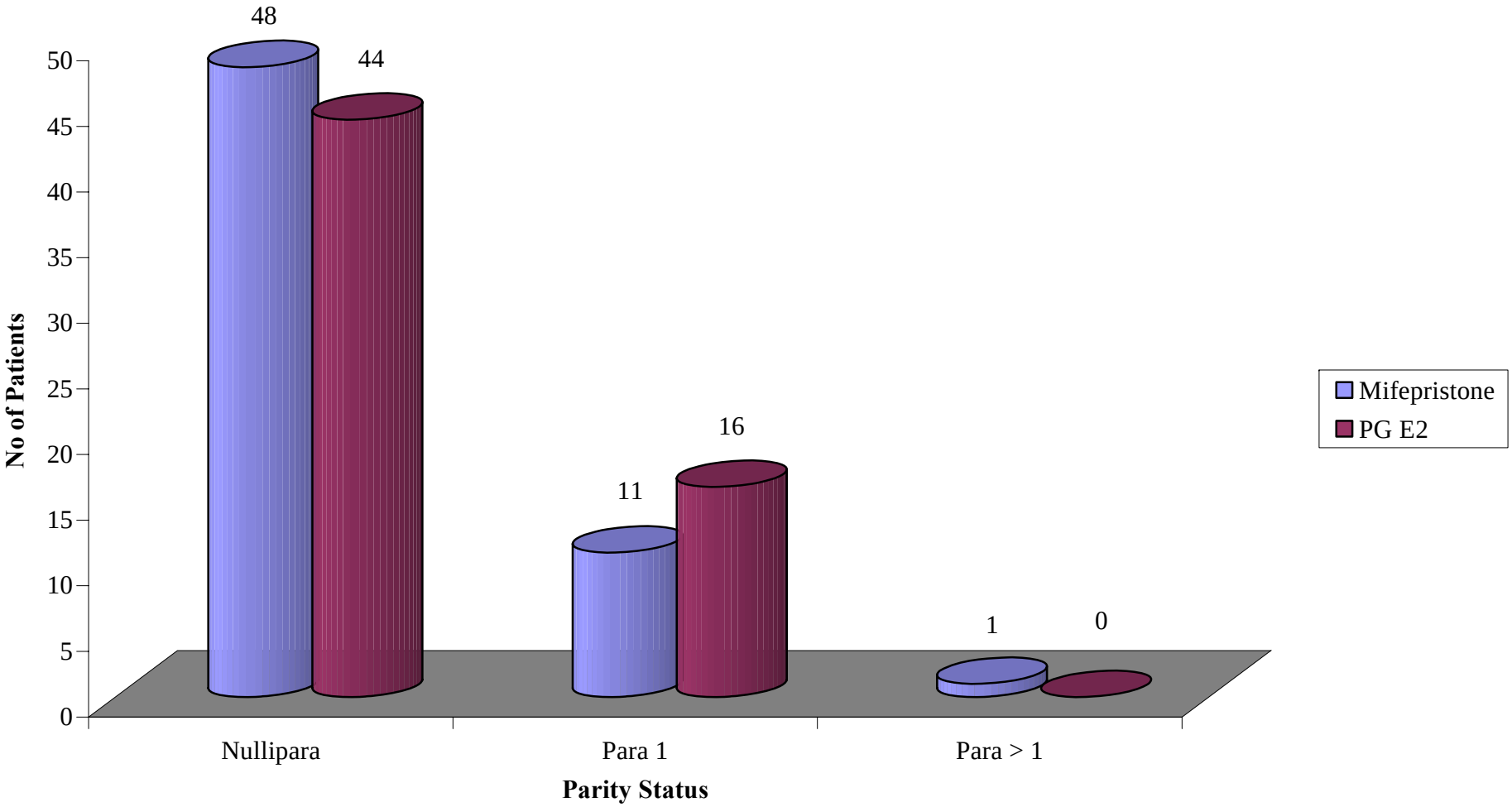


TABLE 4

COMPARISON OF PRE INDUCTION BISHOP SCORE

Pre-induction Bishop score	Study Group (n=60)		Control group (n=60)	
	No	%	No	%
0	12	20.0	25	41.7
1	26	43.3	10	16.7
2	13	21.7	19	31.7
3	9	15.0	6	10.0
Mean ± SD	1.32±0.97		1.10±1.07	

The pre induction Bishop score was comparable in both groups

Fig 5. COMPARISON OF PRE INDUCTION BISHOP SCORE

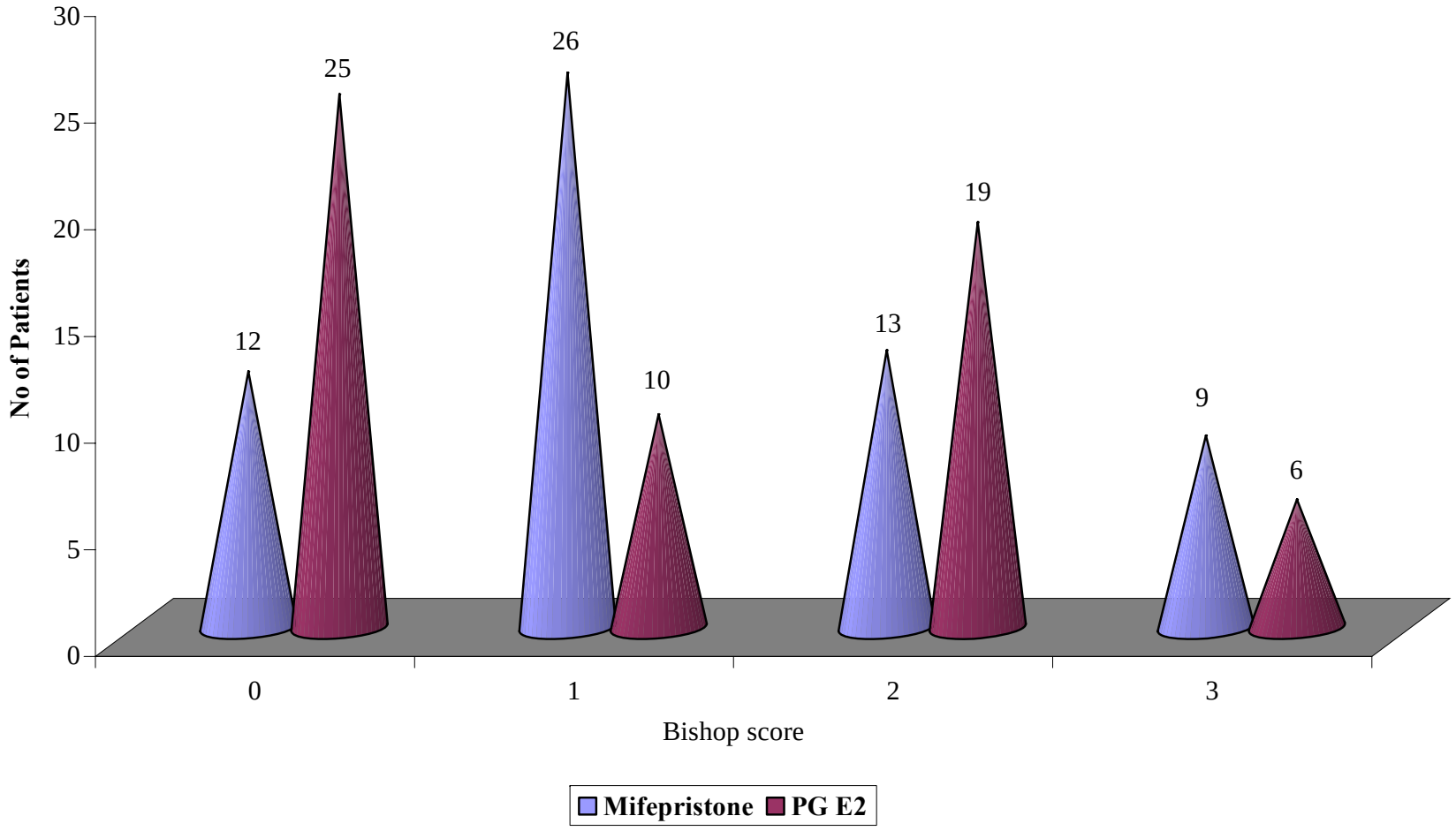


TABLE 5

FAVORABLE IMPROVEMENT IN BISHOP SCORE (6 and more)

	No (n=60)	%	P value
Study group	**46**	**76.6**	**χ^2=30.00;**
Control group	**16**	**26.6**	**P<0.001****

The favorable improvement in Bishop Score was more in the mifepristone treated group when compared with the prostaglandin E2 group

Of the 46 patients - 28 patients had Bishop score 6 during reassessment

Fig 6. FAVORABLE IMPROVEMENT IN BISHOP SCORE (6 and more)

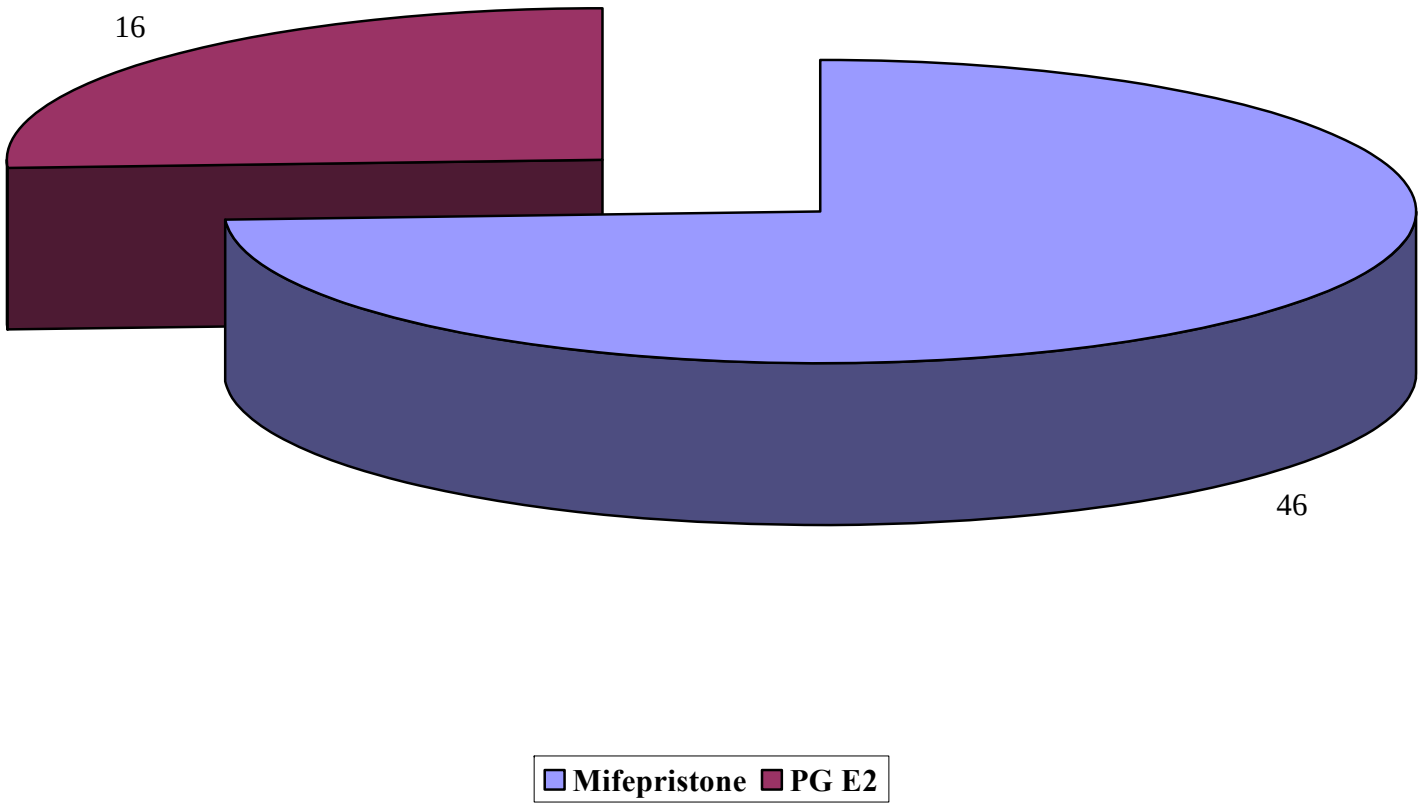


TABLE 6

COMPARISON OF FAVOURABLE IMPROVEMENT IN BISHOP SCORE - NULLIPARA VS PAROUS WOMEN

	Nullipara		Parous women	
	No	**%**	**No**	**%**
Study group	39	81.2	7	58.3
Control group	6	13.6	10	62.5
Inference	χ^2=13.30; P<0.001**			

The favorable improvement in bishop score is more in nullipara when compared to parous women (P<0.001)

In the control group the patients with unfavorable cervix required a second or third dose of PG E2

Fig 7. COMPARISON OF FAVOURABLE IMPROVEMENT IN BISHOP SCORE - NULLIPARA VS PAROUS WOMEN

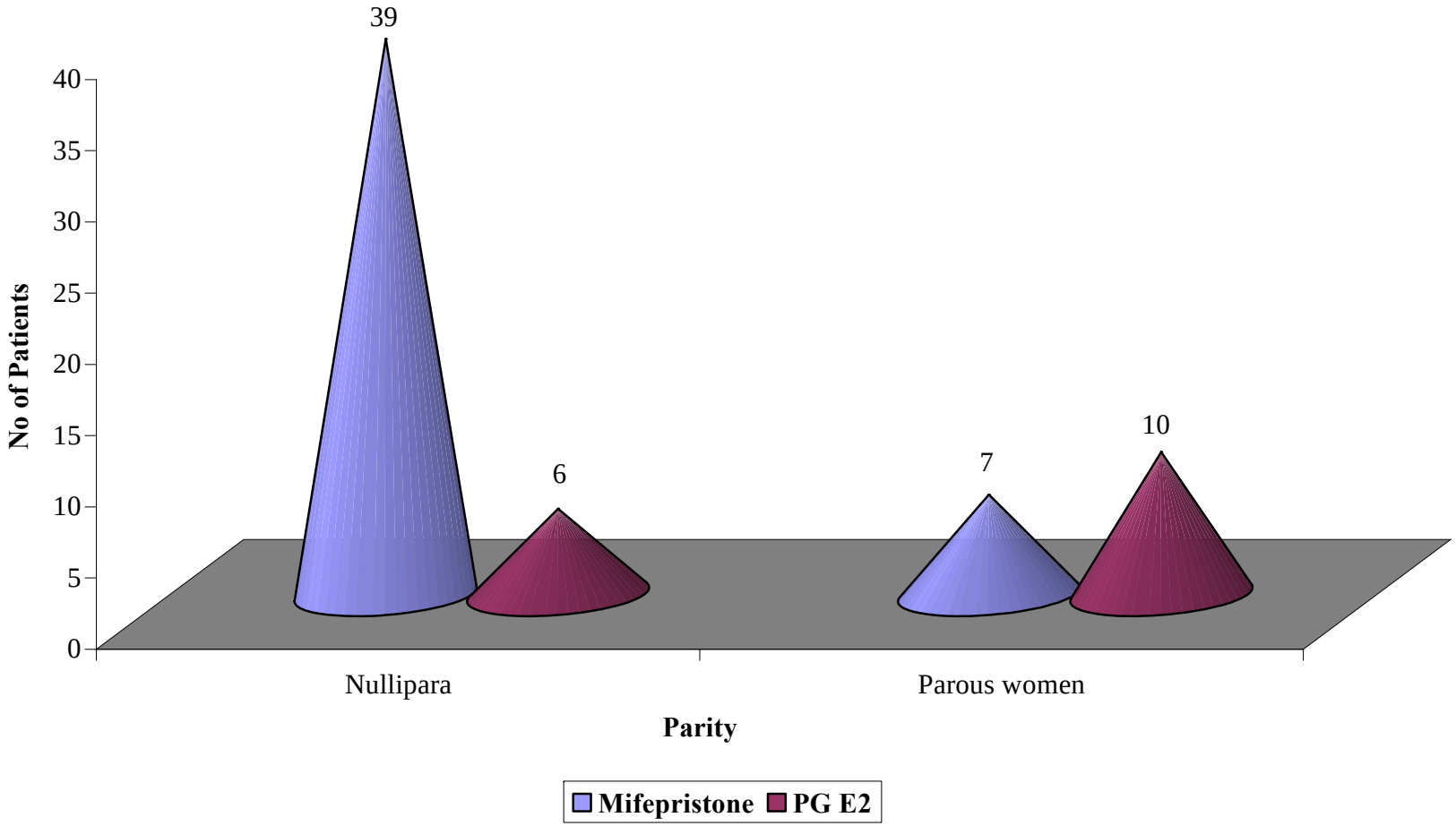


TABLE 7

COMPARISON OF MODE OF DELIVERY

Mode of delivery	Study Group (n=60)		Control group (n=60)	
	No	%	No	%
NVD	20	33.3	14	23.3
VACCUM	20	33.3	16	26.6
FORCEPS ASSISTED	3	5.0	2	3.3
LSCS	17	28.3	28	46.6

Incidence of LSCS is more in control group

(Not statistically significant P= 0.219)

Fig 8. COMPARISON OF MODE OF DELIVERY

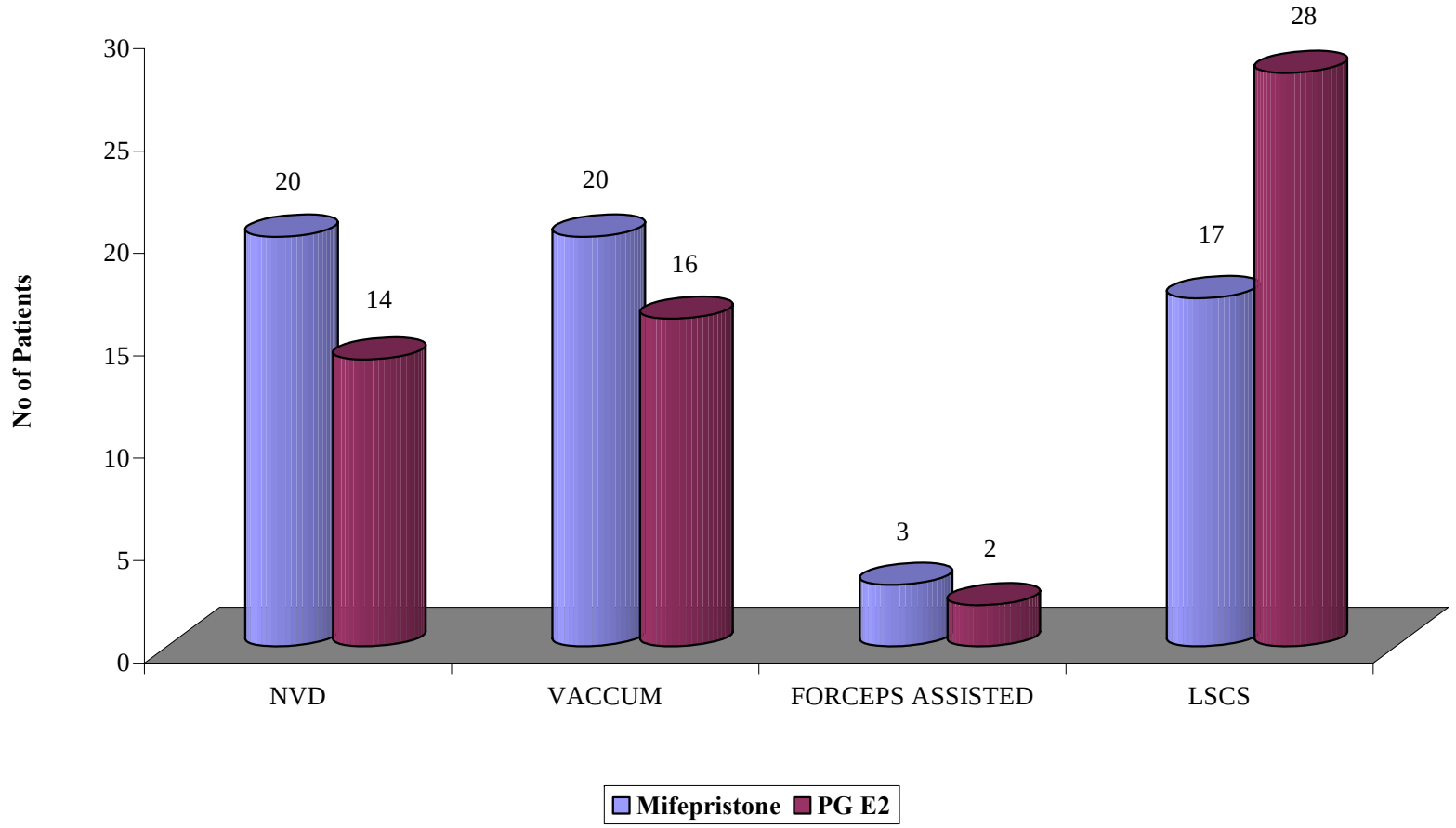


TABLE 8

INDICATION FOR LSCS

	Study Group (n=17)		Control group (n=28)	
	No	**%**	**No**	**%**
Fetal distress	**7**	**41.1**	**14**	**50**
Non progression	**7**	**41.1**	**12**	**42.8**
Meconium stained	**2**	**11**	**2**	**7.1**
Tight cord ar.neck	**1**	**5.9**	**0**	**0**
Total	**17**	**100.0**	**28**	**100.0**

The rate of fetal distress and meconium stained liquor is comparable in both groups

6 infants in the mifepristone group and 4 in the PG E2 group had meconium in utero of which 2 from each group had to be taken up for LSCS

Fig 9. INDICATION FOR LSCS

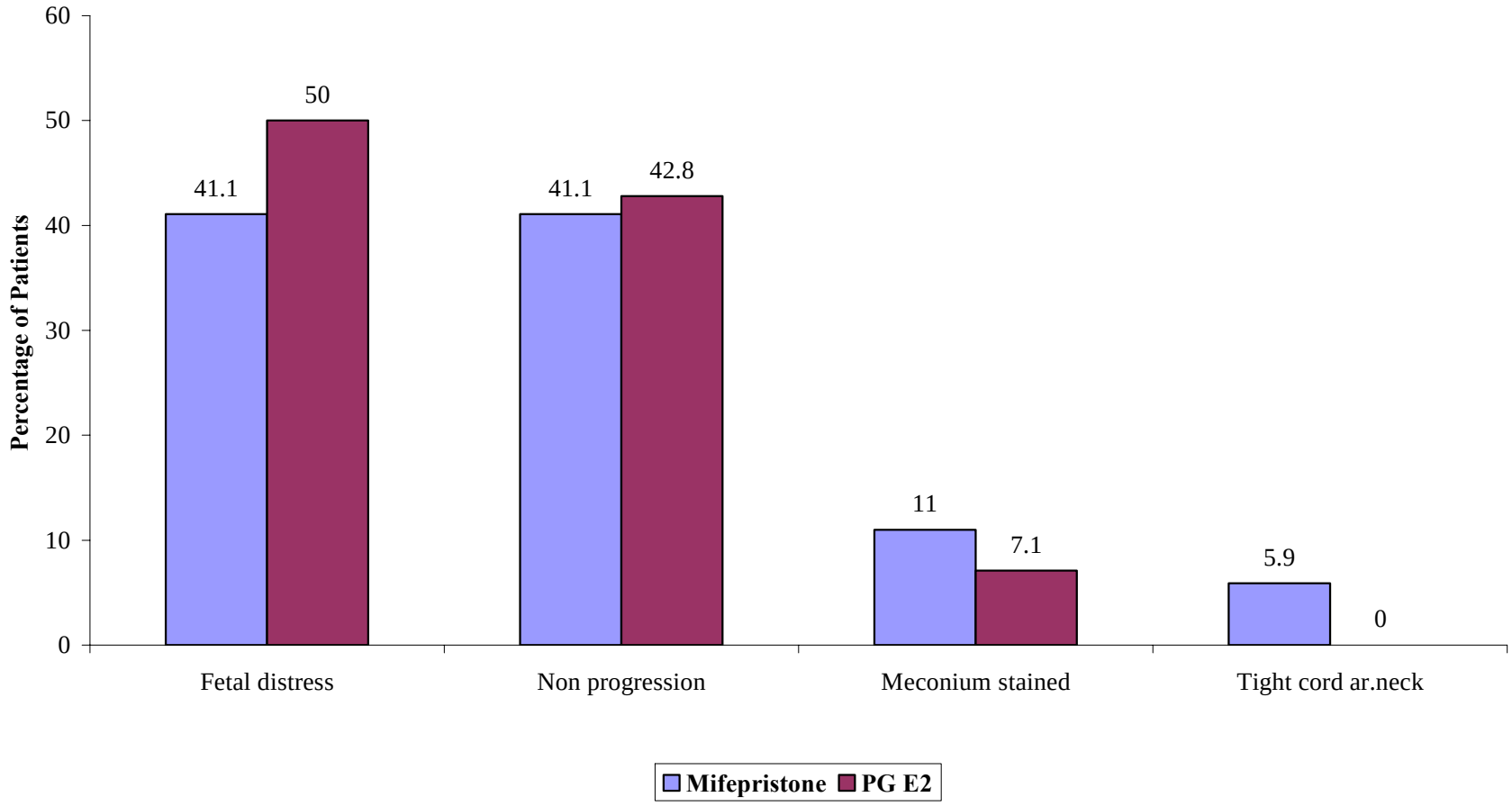


TABLE 9

COMPARISON OF BIRTH WEIGHT OF BABIES

Birth weight (kg)	Study Group (n=60)		Control group (n=60)	
	No	%	No	%
<2.50	9	15.0	9	15.0
2.50-3.00	26	43.3	21	35.0
3.0-3.50	19	31.7	24	40.0
3.50 & above	6	10.0	6	10.0
Mean ± SD	2.93±0.38		2.94±0.39	

Birth weight (kg) is statistically similar between two groups with p=0.842

Fig 10. COMPARISON OF BIRTH WEIGHT OF BABIES

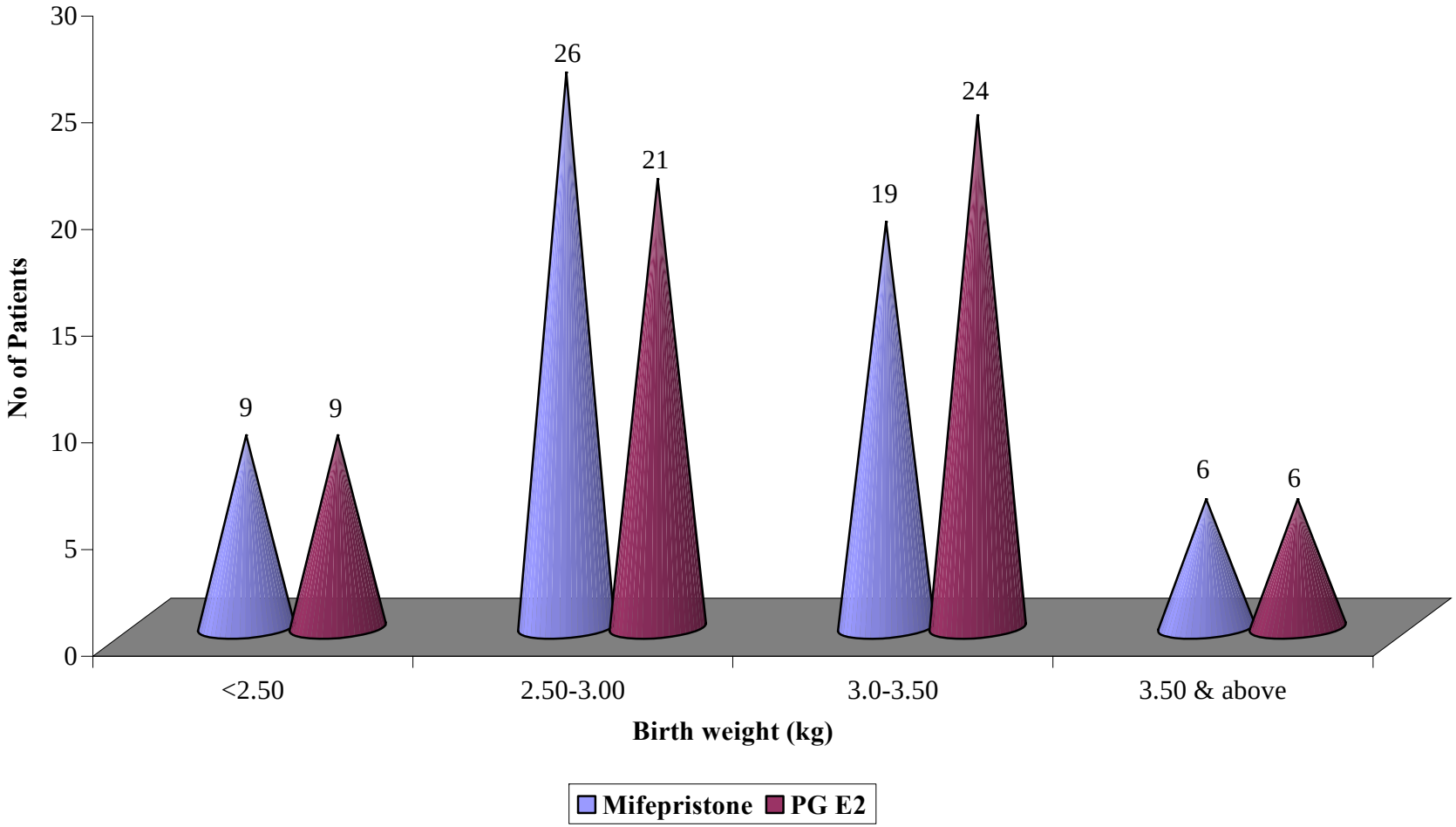


TABLE 10

COMPARISON OF FETAL DISTRESS, NICU ADMISSION AND VENTILATOR SUPPORT

	Study Group (n=60)		Control group (n=60)		P value
	No	%	No	%	
Fetal distress	4	6.7	5	8.3	0.729
NICU admission	2	3.3	1	1.6	0.496
Ventilator support	0	0.0	0	0.0	1.000

The incidence of fetal distress and NICU admission was comparable in both groups

Fig 11. COMPARISON OF UNFAVOURABLE OUTCOME IN NEONATES

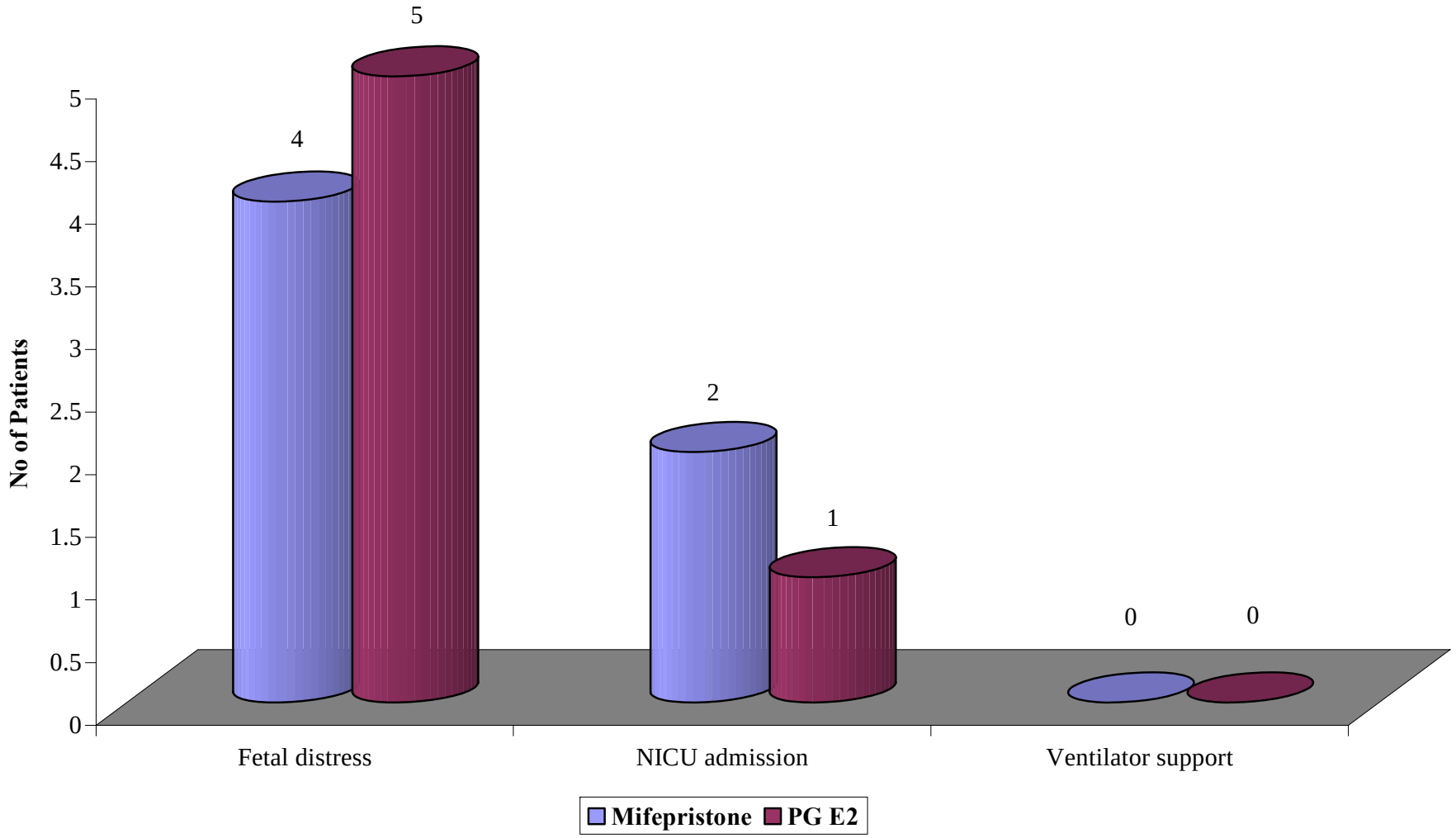


TABLE 11

COMPARISON OF TREATMENT DELIVERY TIME INTERVAL

Delivery Interval Time	Study Group (n=60)		Control group (n=60)	
	No	%	No	%
1-30	7	11.7	21	35.0
31-50	17	28.3	36	60.0
51-70	34	56.7	3	5.0
>70	2	3.3	0	0.0
Mean ± SD	50.74±15.29		35.47±8.39	

Treatment delivery interval time is significantly more in Study group compared to Control group with p<0.001

This can be explained due to the prolonged t (1/2) of mifepristone

Fig 12. COMPARISON OF TREATMENT DELIVERY TIME INTERVAL

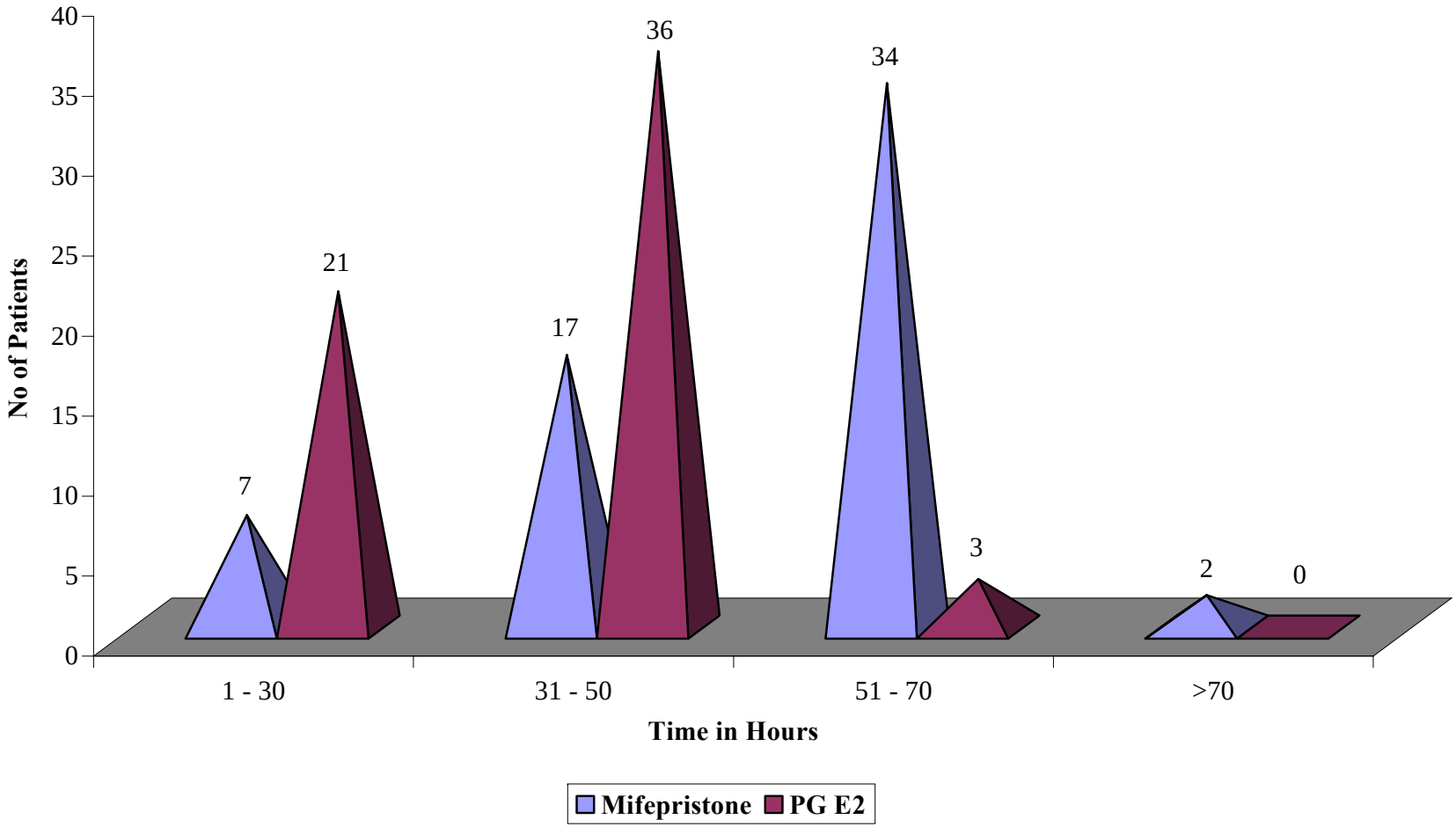


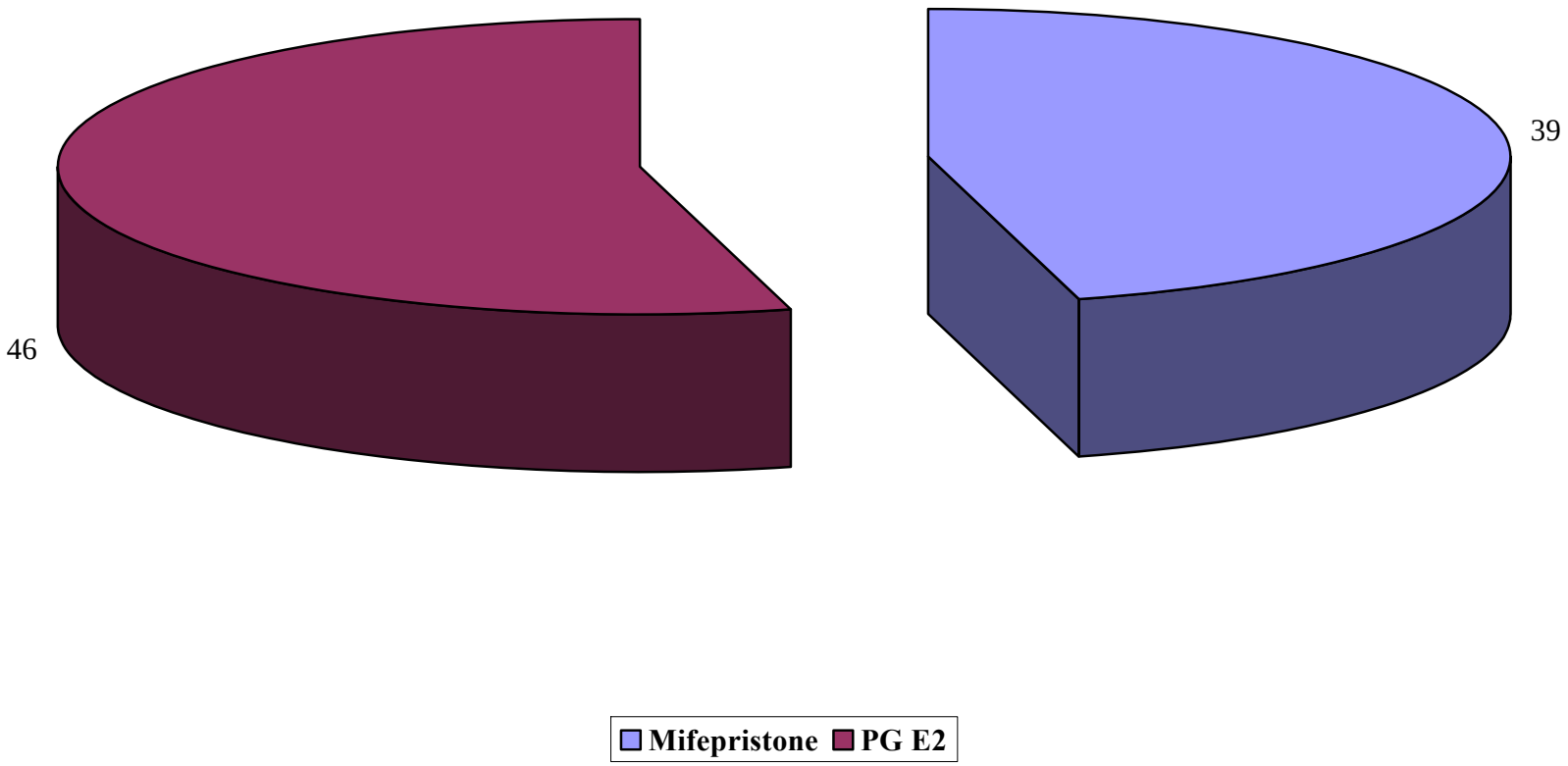
TABLE 12

AUGMENTATION WITH OTHER DRUGS

	No (60)	%
Study group	**39**	**65.0**
Control group	**46**	**76.6**
Inference	**χ^2=1.98; P=0.160**	

There was no difference in the need for augmentation with other drugs in both groups (P not significant)

Fig 13. AUGMENTATION WITH OTHER DRUGS



Discussion

DISCUSSION

The process of labor initiation remains a mystery. It is well known, however, that progesterone is integral in the maintenance of pregnancy. It is hypothesized that anti progestin exposure in pregnancy will enhance the initiation of parturition.

Mifepristone a progesterone antagonist is a steroid compound which may soften the cervix and cause uterine contractions. This medication has been shown to be effective for elective abortions and medical termination of pregnancy during the first trimester. This lead others to study the effect of mifepristone in term pregnancies. Results of these studies hav

.0e demonstrated that mifepristone may ripen the cervix and induce labor while not increasing the risk to the fetus.

In this study, study population comprised of 120 patients with equal no of patients in the study and control group. There were no significant statistical differences between the treatment groups in demographics or medical or obstetrics history.

92 (76.6%) patients were nulliparous, 27 (22.5%) were para 1 (delivered once) and 1 (0.83%) para >1 (delivered more than once). The mean gestational age at treatment initiation was 38.6 in the study group and 38.7 in the control group, with no significant difference across the groups.

The mean bishop score at inclusion was 1.32 in the study group and 1.10 in the control group with no significant differences between the groups. The bishop score was < 2 in 73 patients and > 2 in 47 patients.

The success rate was higher when the Bishop score at inclusion was 3 or 4 (P <0.0001). A study done by Elliot [64] and colleagues compared the effects of 50 mg and 200 mg of oral mifepristone with placebo on cervical ripening and labor induction in primigravid women with unfavorable cervices at term. At a dose of 200 mg, mifepristone resulted in a favorable cervix or spontaneous labor more often than did placebo.

Treatment was successful (onset of labor and/or a bishop score >/= 6 before or at the time of reassessment for study and control group) in 46 (76.6%) women in study group when compared to 16 (26.6%) women in the control group.

There are many studies comparing mifepristone with placebo.

A similar comparison was observed in a study by Wing DA [29] et al who reported that 54 percent normal women given 200 mg Mifepristone daily for two consecutive days went into labor within 72 hours compared with only 18.2 percent of those given a placebo.

In a RCT study done by Berkane [28] et al which compared mifepristone with placebo showed that treatment was successful in about 52.7% of the patients assessable for efficacy with no significant difference among the groups (P=0.73).

A study done by Karl et al stated that mifepristone treated group was successful in 52.7% of patients when compared with placebo. Another randomized control trial by Giacalone [22] et al from France also proved that mifepristone is effective for cervical ripening and reduced the time to delivery when compared with placebo.

39 (81.2%) nulliparous women had favorable improvement in bishop score when compared to 6 (13.6%) parous women. A study done by Nadia [28] et al showed that the relationship between parity and success rate was close to significance (P = 0.053).

The mean treatment to delivery interval was 50.7 hours in the mifepristone treated group when compared to 35.46 hours in the prostaglandin treated group. The difference in the two groups was nearly 15 hours, which is in part due to the 48 hour observation period after mifepristone administration.

A Cochrane review 2009 [30] said that compared to placebo mifepristone treated women were less likely to have an unfavorable cervix at 48 hours (RR – 0.39) or at 96 hours (RR- 0.39). Further the review stated that mifepristone treated women were more likely have delivery within 48 and 96 hours of treatment than with the placebo treated group.

A study done by Frydman[13] et al said that the mean interval between the time of induction and the onset of labor was significantly shorter in the mifepristone treated group.

A study done by Berkane [28] et al showed that as the dose of mifepristone increased the interval between the treatment and onset of labor, and between the treatment and delivery tended to be shorter. The difference was significant between 600mg mifepristone and placebo

A study done by Karl et al stated that labor was prolonged in the groups who received lower doses of mifepristone than those who received 400 or 600 mg. A study

done by Josie [62] et al stated that women treated with mifepristone are more likely to have a favorable cervix within 48 to 96 hours when compared with placebo.

Another study by Zhonghua et al from Beijing stated that the cervical ripening ratio was 100% in the mifepristone treated group.

Another study from Sweden [14], department of women and child health says that the median time taken from the onset unto delivery is relatively lower in groups with mifepristone than the control group.A similar French study [15] stated that the onset of labor was one day earlier in the mifepristone treated group when compared with placebo.

The rate of normal and assisted vaginal deliveries was 66.6% in the mifepristone treated group when compared to 49.9% in the prostaglandin treated group with a significant P value. A similar comparison was observed by an RCT by Wing et al [29] who stated that 87.5% women in the mifepristone treated group were delivered vaginally 48 hours after the start of treatment than 70% in the placebo treated group.

Another study by Zhonghua et al from Beijing stated that the incidence of vaginal delivery was 80.8% in the mifepristone treated group.

The rate of caesarean deliveries (28.3%) was comparably less in the mifepristone treated group than the prostaglandin treated group (46.6%).

A Cochrane review [30] in 2009 said that the mifepristone treated women were less to undergo caesarean section (RR -0.71). Another prospective study done by Mc

gill [16] et al United Kingdom showed that the rate of caesarean section was significantly lower among women induced with mifepristone alone.

A similar comparison was found in a study by Josie et al who stated that the mifepristone treated women were less likely to undergo caesarean section

Of the 17 (28.3%) mifepristone treated women who underwent caesarean section 7 (41%) cases were indicated for fetal distress. 1 (5.8%) case had tight loop of cord around the neck. Among the 28 (46.6%) prostaglandin treated women 14 (50%) cases were for fetal distress. A similar comparison was observed in a study Wing [29] et al with about 60% of cases in the mifepristone treated group was for fetal distress.

An analysis of the effect of parity on outcomes of induction revealed that a mean of 22.8% of nulliparous women delivered vaginally when compared to a mean of 50% parous women. This is comparable to the study by Berkane [28] et al which stated that the rate of vaginal delivery increases with parity.

The mean induction delivery time interval for the mifepristone treated nulliparous women was 52.8 hours when compared to 36.45 hours in the prostaglandin treated nulliparous women. A RCT done by Guberman [28]et al said that the duration of labor was longer for nulliparous women when compared with the parous subjects irrespective of the mode of treatment.

Meconium passage in utero occurred in 6 (10%) infants of the mifepristone treated group which is more when compared to 4 (6.6%) infants in the prostaglandin treated group which is similar to a study by Wing [29] et al where meconium passage was 9.1% in the mifepristone treated group.

Abnormal FHR pattern was found were found in 7 (11.6%) cases of the mifepristone treated group and 14 (23%) cases of the prostaglandin treated groups.

A Cochrane review [30] 2009 stated that the rate of abnormal FHR pattern was higher in the mifepristone treated group. Another study by Wing [29] et al stated than the rate of fetal distress was higher in the mifepristone treated group.

The birth weight and rate of Apgar score at 1 min and at 5 min was statistically similar in the study and control group. Two (3.3%) infants in the study group and one (1.6%) infant in the control group required admission in NICU. A study by Guberman [28] et al stated that the rate of NICU admission and the need for resuscitation was higher in the mifepristone treated group

A Cochrane review [30] in 2009 said that the incidence of neonatal hypoglycemia might be more common after exposure to mifepristone (it antagonizes the action of glucocorticoids as well as the action of progesterone).

Another study done by Karl et al stated that there was no difference in fetal tolerability and the rate of fetal distress. A study done by clamart [15] et al from France says that mifepristone appears safe and useful with no adverse effects on the fetus or mother

There was no significant difference in the maternal heart rate (beats/min) or systolic or diastolic blood pressure on day 0 , day 1 or day 2 of treatment in both the study and control group which is comparable to a study by Nadia [28] et al where in there was no significant difference. Another study by Wing et al also stated that there were no adverse uterine abnormalities or maternal complications observed in the mifepristone treated groups.

The need for augmentation with other uterotonic agents was less with mifepristone treated groups (65%) when compared with the prostaglandin treated groups (76.6%) though not statistically significant.

A RCT done by Frydman [13] et al suggested that the need for oxytocin was much lesser in the mifepristone treated group when compared with placebo. Another French [15] study stated that women treated with mifepristone had more spontaneous labor and lesser doses of augmentation.

Another study by Wing [29] et al stated that the dose and amount of oxytocin required was lesser in the mifepristone treated group

Conclusion

CONCLUSION

Mifepristone has proved very useful for medical abortion in the first and second trimester termination of pregnancy. It has an established role as an effective cervical priming agent. This effect is now utilized for cervical ripening in term pregnancies. Mifepristone is well tolerated by pregnant women and the efficacy which has been proved in many trials.

There are a few reports in the literature describing the effect of mifepristone as a pre induction cervical ripening agent for term pregnancies. However available data do show that mifepristone is better than a placebo at ripening the cervix or inducing labor.

In our study we compared the effect of mifepristone with prostaglandin E2 gel.

In our study we found that mifepristone as a pre induction cervical ripening agent had better proven efficacy especially in primigravid women as similarly proved by various other earlier standard trials. The need for augmentation with other oxytocics was also reduced in the mifepristone treated groups.

Theoretically, mifepristone has appeal as a method of inducing labor in women with previous caesarean section as it does not involve administering exogenous oxytocic drugs that have potential to over stimulate. There is evidence of a possible reduction in the incidence of caesarean section following mifepristone treatment (compared to placebo) that would justify further trials quoted as per the reviews of Cochrane [30] 2009.

This study was a pilot study to assess the efficacy of mifepristone as a pre induction cervical ripening agent in term pregnancies and to study its adverse effects on mother and fetus. The results are encouraging with no significant adverse effects on mother and fetus. Further efforts can be put forth to probe the study further and prove the effectiveness of the drug and its efficacy. Further studies can be done comparing 200 mg of mifepristone with 400 mg or even higher doses if found favorable. It promises to be a more compliant drug in near future.

Bibliography

BIBLIOGRAPHY

1. de Ribes C. De l'Accouchement Provoque, Dilatation du Canal Genital a l'Aide de Ballons Introduits dans la Cavite Uterine Pendant la Grossesse. Paris, Steinheil, 1988.
2. Paré A. De la Generation de l'Homme. 1550
3. Graham H. Eternal Eve: The History of Gynecology and Obstetrics. London, T. Brun, 1950
4. Denman T. An Introduction to the Practice of Midwifery. London, J. Johnson, 1794.
5. Eden TW. Review: A Manual of Midwifery, 3rd ed. Lancet 1912; 1:1064
6. Dale HH. On some physiological actions of ergot. J Physiol 1906O; 34:163–206
7. Bell WB. The pituitary body. BMJ 1909; 2:1609–13
8. Page EW. Response of human pregnant uterus to pitocin tannate in oil. Proc Soc Exp Biol 1943; 52:195–7.
9. Theobald GW. The use of posterior pituitary extracts in physiological amounts in obstetrics. BMJ 1948; 11:123–7.
10. Karim SMM, Trussele RR, Patel RC, Hillier K. Response of pregnant human uterus to prostaglandin F2 alphainduction of labour. BMJ 1968; IV: 621–3
11. Keirse MJNC. Prostaglandins in preinduction cervical ripening. Meta-analysis of world-wide clinical experience. J Reprod Med 1993; 38(Suppl):69–98.
12. Sanchez-Ramos L, Kaunitz AM, DelValle GO, et al. Labor induction with the prostaglandin E1 methyl analogue misoprostol versus oxytocin: A randomized trial. Obstet Gynecol 1993; 81:332–6.

13. Labor induction in women at term with mifepristone (RU 486): a double-blind, randomized, placebo-controlled study. Frydman R et al. Obstet Gynecol. (1992)Lelaidier C et al. Mifepristone for labour induction after previous caesarean section. Br J Obstet Gynaecol. (1994)
14. Stenlund PM et al. Induction of labor with mifepristone--a randomized, double-blind study versus placebo. Acta Obstet Gynecol Scand. (1999)
15. Lelaidier C et al The value of RU-486 (mifepristone) in medical indications of the induction of labor at term. Results of a double-blind randomized prospective study (RU-486 versus placebo)].. J Gynecol Obstet Biol Reprod (Paris). (1993)
16. McGill J. Shetty A. Mifepristone and misoprostol in the induction of labor at term. International Journal of Gynaecology & Obstetrics. 96(2):80-4, 2007 Feb
17. Neilson JP, Mifepristone for induction of labour. Cochrane Database Syst Rev 2002; 2:CD002865.
18. Tenore JL. Methods for cervical ripening and induction of labor.Am Fam Physician. 2003 May 15; 67(10):2123-8.
19. Edwards MS. Mifepristone: cervical ripening and induction of labor.Clin Obstet Gynecol. 1996 Jun; 39(2):469-73.
20. Dodd J, Induction of labour for women with a previous Caesarean birth: a systematic review of the literature. Aust N Z J Obstet Gynaecol. 2004 Oct; 44(5):392-5.
21. Caughey AB, Maternal and neonatal outcomes of elective induction of labor. Evid Rep Technol Assess (Full Rep). 2009 Mar ;(176):1-257.

22. Giacalone PL, Cervical ripening with mifepristone before labor induction: a randomized study. Obstet Gynecol. 1998 Oct;92(4 Pt 1):487-92
23. Poma PA. Cervical ripening: a review and recommendations for clinical practice. J Reprod Med 1999; 44:657–68.
24. Krammer J, Williams MC, Sawai SK, et al. Pre-induction cervical ripening: a randomized comparison of two methods. Obstet Gynecol 1995; 85:614– 8.
25. Riskin-Mashiah S, Wilkins I. Cervical ripening. Obstet Gynecol Clin North Am 1999;26: 243– 57.
26. Heikinheimo. The pharmacokinetics of mifepristone in humans reveals insights into differential mechanisms of antiprogestin action". Contraception 68 (6) 2003: 421-6.
27. American College of Obstetricians and Gynecologists. Induction and augmentation of labor. ACOG Technical Bulletin No. 110. Washington, DC7 American College of Obstetricians and Gynecologists; 1987.
28. Berkane N, Verstraete L, Uzan S, et al. Use of mifepristone to ripen the cervix and induce labor in term pregnancies. Am J Obstet Gynecol. 2005; 192(1):114-120.
29. Wing DA, Guberman C, Fassett M. A randomized comparison of oral mifepristone to intravenous oxytocin for labor induction in women with prelabor rupture of membranes beyond 36 weeks' gestation. Am J Obstet Gynecol. 2005;192(2):445-451.
30. Hapangama D, Neilson JP. Mifepristone for induction of labour. Cochrane Database Syst Rev. 2009 ;(3):CD002865.
31. Committee opinion. Induction of labor for vaginal birth after cesarean delivery. Obstet.Gynecol. 2002; 99:679-80. SOGC clinical practice guidelines.

Guidelines for vaginal birth after previous caesarean birth. Number 155 (Replaces guideline Number 147), February 2005. Int.J.Gynaecol.Obstet. 2005; 89:319-31.

32. ACOG Committee Opinion No. 342: induction of labor for vaginal birth after cesarean delivery. Obstet.Gynecol. 2006; 108:465-8.
33. Vaginal birth after previous cesarean section. Journal of Midwifery & Womens Health 2004; 49:68-75.
34. Apgar BS. Current trends in cervical ripening and labor induction. Am.Fam.Physician 1999; 60:418-20.
35. Baulieu EE. The combined use of prostaglandin and antiprogestin in human fertility control. Adv.Prostaglandin Thromboxane Leukot.Res. 1995; 23:55-62.
36. Baxley EG. Labor induction: A decade of change. American Family Physician 2003; 67:2076-+.
37. Brennand J,.Greer I. Induction of labour: new horizons. Hosp.Med. 1998; 59:856-60.
38. Carr CA, Burkhardt P, Avery M. Vaginal birth after cesarean birth: A national survey of US midwifery practice. Journal of Midwifery & Womens Health 2002; 47:347-52.
39. Crane JM,.Young DC. Induction of labour with a favourable cervix and/or pre-labour rupture of membranes. Best.Pract.Res.Clin.Obstet.Gynaecol. 2003; 17:795-809.
40. Crane JM, Butler B, Young DC, Hannah ME. Misoprostol compared with prostaglandin E2 for labour induction in women at term with intact

membranes and unfavourable cervix: a systematic review. BJOG. 2006; 113:1366-76.

41. Dare MR, Middleton P, Crowther CA, Flenady VJ, Varatharaju B. Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more). Cochrane Database of Systematic Reviews 2006.
42. Dodd J,.Crowther C. Induction of labour for women with a previous Caesarean birth: a systematic review of the literature. Aust.N.Z.J.Obstet.Gynaecol. 2004;44:392-5.
43. Duff P. Premature rupture of the membranes in term patients. Seminars in Perinatology 1996; 20:401-8.
44. El Refaey H,.Jauniaux E. Methods of induction of labour. Curr.Opin.Obstet.Gynecol. 1997; 9:375-8.
45. Hadi H. Cervical ripening and labor induction: Clinical guidelines. Clinical Obstetrics and Gynecology 2000; 43:524-36.
46. Harman JH, Jr.,.Kim A. Current trends in cervical ripening and labor induction. Am.Fam.Physician 1999; 60:477-84.
47. Justus HG. Induction of labour with an unfavourable cervix. Best.Pract.Res.Clin.Obstet. Gynaecol. 2003; 17:777-94.
48. Morey SS. ACOG develops guidelines for induction of labor. Am.Fam.Physician 2000; 62:445.
49. Mozurkewich E. Prelabor rupture of membranes at term: induction techniques. Clin.Obstet.Gynecol. 2006; 49:672-83.
50. Peek MJ. Drugs for obstetric conditions. Best Practice & Research in Clinical Obstetrics & 2001; 15:999-1011.

51. Ramsey PS, Ramin KD, Ramin SM. Labor induction. Current Opinion in Obstetrics & Gynecology 2000; 12:463-73.
52. Rayburn WF. Preinduction cervical ripening: basis and methods of current practice. Obstet.Gynecol.Surv. 2002; 57:683-92.
53. Reichler A, Romem Y, Divon MY. Induction of labor. Curr.Opin.Obstet.Gynecol. 1995; 7:432-6.
54. Sanchez-Ramos L,.Hsieh E. Pharmacologic methods for cervical ripening and labor induction. Curr.Womens Health Rep. 2003; 3:55-60.
55. Sitruk-Ware R. Mifepristone and misoprostol sequential regimen side effects, complications and safety. Contraception 2006; 74:48-55.
56. Summers L. Methods of cervical ripening and labor induction. J.Nurse Midwifery 1997; 42:71-85.
57. Surbek DV, Hosli I, Holzgreve W. [Current aspects of labor induction]. Ther.Umsch. 2002; 59:650-9.
58. Taylor SJ,.Armour CL. Cost implications in the management of induction of labour. Pharmacoeconomics 1997; 12:547-54.
59. Tinelli A, Tinelli R, Tinelli FG. [Induction of labour: which method to use?]. Minerva Ginecol. 2003; 55:463-82.
60. Yulzari-Roll V, Hod M, Bar J. [New developments in labor induction]. Harefuah 2002; 141:369-73, 408.
61. Hofmeyr GJ, Misoprostol for induction of labour: a systematic review.Br J Obstet Gynaecol. 1999 Aug; 106(8):798-803. Review.
62. Hapangama D, Mifepristone for induction of labour. Cochrane Database Syst Rev. 2009 Jul 8;(3)

63. F. Cadepong, RU486 (MIFEPRISTONE): Mechanisms of Action and Clinical Uses. Annual Review of Medicine, Vol. 48: 129-156 (Volume publication date February 1997)

64. Elliott CL, The effects of mifepristone on cervical ripening and labor induction in primigravidae. Obstet Gynecol. 1998 Nov; 92(5):804-9.

Annexures

PSG Institute of Medical Science and Research, Coimbatore

INFORMED CONSENT

I, Dr.P.Uma Devi, MD., (OG) post graduate from the department of Obstetrics and Gynaecology of the PSG Institute of Medical Sciences & Research (PSG IMS&R), am carrying out a study titled

Is oral mifepristone as effective as vaginal prostaglandin E2 in pre induction cervical ripening at term gestation in normal and uncomplicated pregnancies?

Under the aegis of the Department of Obstetrics and Gynaecology, PSG IMSR.

The objectives of this study are:

To assess the effectiveness of oral mifepristone as a pre induction cervical ripening agent in comparison with vaginal prostaglandin E2 gel by assessing the favourable improvement in Bishop's score

This goal of the study is

To study whether oral mifepristone is as effective as vaginal prostaglandin E2 gel for pre induction cervical ripening in term viable uncomplicated pregnancies

Sample size: 100.
Respondents are all term antenatal patients who are coming for checkups/ delivery in PSG Hospitals – Labour ward, Coimbatore

We request you to kindly cooperate with us in this study. We propose collect background information and other relevant details related to this study. We will be carrying out Initial interview to assess for the risk factors (if any) for the patient and following inclusion of the patient into the study general and systemic examination with per vaginal examination for assessment of pre induction bishop score will be done. Subsequently non stress test for assessment of foetal well being will be done followed by doing repeat per vaginal examination for assessing the favourability of bishop score.

If you are uncomfortable in answering any of our questions during the course of the interview / blood sample collection, **you have the right to withdraw from the interview / study at anytime.** You will **NOT** be paid any remuneration for the time you spend with us for this interview / study. The information provided by you will be kept in strict confidence. Under no circumstances shall we reveal the identity of the respondent or their families to anyone. The information that we collect shall be used for approved research purposes only.

Consent: The above information regarding the study, has been read by me/ read to me, and has been explained to me by the investigators from the PSG IMS&R. Having understood the same, I hereby give my consent to them to interview me. I affixing my signature / left thumb impression to indicate my consent and willingness to cooperate in this study.

Respondent ID: _____. Signature / Left thumb impression of the Respondent. Signature of the Investigator with date

Signature of the witness

CASE PROFORMA

Name **Age** **Hospital no**

LMP **EDD**

Gestational age

DOA **DOD**

Obstetric formula

Chief complaints

Pain + / -

Bleeding PV + / -

Leaking PV + / -

Foetal movments

Yes / no

Menstrual H/o

Days -

Cycles – regular / irregular

Marital H/o

Married since

Booked / unbooked

Antenatal complications

PIH /GDM / IUGR / preterm / anaemia / oligohydramnios/ previous LSCS - ind

Past H/o

Hypertension / DM / BA / PTB

Examination

General examination

Pallor	no / mild / severe
Edema	+ / -
Breast	normal / abnormal
Thyroid	palpable / not palpable
Height	weight
Pulse rate	Blood pressure

Systemic examination

CVS

RS

P/A – Height of uterus

Lie / presentation

Presenting part

Engaged / unengaged

FHR

NST

P/S – leaking + / - ; if (+) colour

P/V – cervix – Consistency

Position

Effacement

Membrane status

Station

Bishop score (before induction)

Investigations

Hb

RBS

Urine routine

Blood grouping

HIV

HbsAg

USG

GA by LMP / USG

EFW

AFI

Presentation

Labour

Spontaneous

Induction – following induction daily NST monitoring and 4th hourly FHR monitoring is essential

Induced with

1. PGE2 gel

Gel kept at ------ on -------. Reassessment at ------

P/V during reassessment

cervix – Consistency

Position

Effacement

Membrane status

Station

Bishop score (after induction)

2. Mifepristone

Drug given at --------- on ----------.

Day 1 – NST –

FHR

Day 2 – NST –

FHR

Reassessment at ---------- on ----------

P/V during reassessment

cervix – Consistency

Position

Effacement

Membrane status

Station

Bishop score (after induction)

Risk factors – low risk / high risk

Duration of stages

I

II

III

Mode of delivery

Normal vaginal delivery + / - episiotomy

Vaccum assisted vaginal delivery + /- episiotomy

Forceps assisted vaginal delivery

LSCS

Baby details

APGAR – 1 min - 5 min –

Resuscitation needed or not

NICU admission needed or not

Ventilatory support needed or not